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ORIGINAL RESEARCH

Prasugrel-Based De-Escalation in Patients With Acute Coronary Syndrome According to Renal Function

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ABSTRACT

BACKGROUND Patients with coronary artery disease and impaired renal function are at higher risk for both bleeding and ischemic adverse events after percutaneous coronary intervention (PCI).

OBJECTIVES This study assessed the efficacy and safety of a prasugrel-based de-escalation strategy in patients with impaired renal function.

METHODS We conducted a post hoc analysis of the HOST-REDUCE-POLYTECH-ACS study. Patients with available estimated glomerular filtration rate (eGFR) (n = 2,311) were categorized into 3 groups. (high eGFR: >90 mL/min; intermediate eGFR: 60 to 90 mL/min; and low eGFR: <60 mL/min). The end points were bleeding outcomes (Bleeding Academic Research Consortium type 2 or higher), ischemic outcomes (cardiovascular death, myocardial infarction, stent thrombosis, repeated revascularization, and ischemic stroke), and net adverse clinical event (including any clinical event) at 1-year follow-up.

RESULTS Prasugrel de-escalation was beneficial regardless of baseline renal function (*P* for interaction = 0.508). The relative reduction in bleeding risk from prasugrel de-escalation was higher in the low eGFR group than in both the intermediate and high eGFR groups (relative reductions, respectively: 64% (HR: 0.36; 95% CI: 0.15-0.83) vs 50% (HR: 0.50; 95% CI: 0.28-0.90) and 52% (HR: 0.48; 95% CI: 0.21-1.13) (*P* for interaction = 0.646). Ischemic risk from prasgurel de-escalation was not significant in all eGFR groups (HR: 1.18 [95% CI: 0.47-2.98], HR: 0.95 [95% CI: 0.53-1.69], and HR: 0.61 [95% CI: 0.26-1.39]) (*P* for interaction = 0.119).

CONCLUSIONS In patients with acute coronary syndrome receiving PCI, prasugrel dose de-escalation was beneficial regardless of the baseline renal function. (JACC: Asia 2023;3:51-61) © 2023 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome

BARC = bleeding Academic Research Consortium

CKD = chronic kidney disease

eGFR = estimated glomerular filtration rate

MI = myocardial infarction

NACE = net adverse clinical event(s)

PCI = percutaneous coronary intervention

Patients with chronic kidney disease (CKD) who receive percutaneous coronary intervention (PCI) represent a challenging subset of patients due to coexisting high bleeding and ischemic risk.[1-3] In those with CKD presenting as acute coronary syndrome (ACS), the risk of adverse clinical events is even higher, emphasizing the importance of optimal antiplatelet therapy.[1-5] Prasugrel is a potent $P2Y_{12}$ inhibitor that has been shown to reduce ischemic outcomes in patients with ACS. Although previous studies reported superior thrombotic outcomes of potent $P2Y_{12}$ inhibitors regardless of renal function, the increased bleeding risk remains a major concern.[6,7] Moreover, bleeding complications after PCI have been shown to be independently associated with mortality.[8,9] To balance the beneficial effect of potent $P2Y_{12}$ inhibitors with reduced bleeding risk, a de-escalation strategy may be a feasible option in patients with decreased renal function.

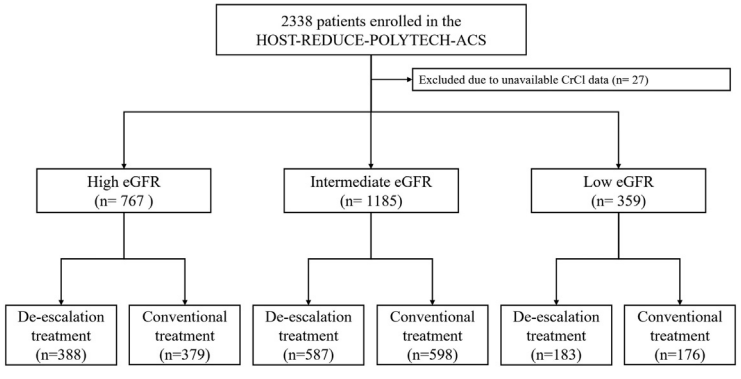
Recently, the HOST-REDUCE-POLYTECH-ACS (Harmonizing Optimal Strategy for Treatment of Coronary Artery Diseases Trial-Comparison of Reduction of Prasugrel Dose and Polymer Technology in ACS Patients; NCT02193971) reported the benefit of prasugrel-based dose de-escalation in ACS patients receiving PCI.[10] In the trial, dose de-escalation of prasugrel significantly reduced the risk of bleeding without any increase in ischemic outcomes. However, it is unknown whether the beneficial effect of prasugrel dose de-escalation is consistent according to renal function, especially in those with depressed renal function, who are at higher risk for both bleeding and ischemic risks. Therefore, we performed a post hoc analysis of the HOST-REDUCE-POLYTECH-ACS trial to evaluate the effect of prasugrel dose de-escalation according to renal function.

METHODS

STUDY OVERVIEW. This study is a post hoc analysis of the HOST-REDUCE-POLYTECH-ACS trial. The HOST-REDUCE-POLYTECH-ACS study was a multicenter randomized controlled trial conducted in 35 sites in Korea that randomized patients diagnosed with ACS and receiving PCI to prasugrel-based de-escalation or prasugrel-based conventional dual antiplatelet therapy. The detailed trial design, inclusion and exclusion criteria, and primary results have been reported previously.[10,11] All patients gave written informed consent for participation in the study before randomization. The study complied with the provisions of the Declaration of Helsinki and was approved by the institutional ethics committee of each participating site.

After the initial coronary angiogram, patients were randomized to the de-escalation group or the conventional group. All patients in both groups were prescribed with 100 mg aspirin daily with 10 mg prasugrel daily until the 1-month follow-up. After the first month, patients in the de-escalation group received a deescalated prasugrel dose of 5 mg, and patients in the conventional group received the conventional 10 mg daily dose. Clinical follow-up was performed until 12 months after the index PCI.

FIGURE 1 Flowchart of Patient Selection



A total of 2,311 patients were included for the present analysis. Patients were categorized into 3 groups according to renal function (estimated glomerular filtration rate [eGFR] above 90 mL/min (high eGFR), eGFR from 60 to 90 mL/min (intermediate eGFR), and eGFR below 60 mL/min (low eGFR)). CrCl = creatinine clearance.

TABLE 1 Baseline Characteristics Stratified by Renal Function and Antiplatelet Therapy Strategy

	High eGFR (n = 767)			Intermediate eGFR (n = 1,185)			Low eGFR (n = 359)		
	De-Escalation (n = 388)	Conventional (n = 379)	*P* Value	De-Escalation (n = 587)	Conventional (n = 598)	*P* Value	De-escalation (n = 183)	Conventional (n = 176)	*P* Value
Mean eGFR, mL/min	108.3	107.3	0.440	75.2	76.0	0.107	47.3	47.9	0.722
Age, y	51.9 ± 7.8	52.1 ± 7.8	0.618	61.1 ± 7.2	60.8 ± 7.6	0.581	65.8 ± 6.6	67.4 ± 5.5	0.018
Male	365 (94.1)	363 (95.8)	0.282	532 (90.6)	521 (87.1)	0.055	142 (77.6)	140 (79.5)	0.700
BMI, kg/m^2	26.2 ± 3.0	26.1 ± 3.0	0.707	25.4 ± 2.6	25.6 ± 2.6	0.386	25.5 ± 2.5	25.8 ± 3.4	0.333
Hypertension	213 (54.9	204 (53.8)	0.772	370 (63.1)	392 (65.6)	0.386	143 (78.1)	136 (77.3)	0.899
Diabetes mellitus	158 (40.7)	144 (38.0)	0.440	239 (40.7)	235 (39.3)	0.618	111 (60.7)	92 (52.3)	0.112
Dyslipidemia	307 (79.1)	294 (77.6)	0.661	442 (75.3)	472 (78.9))	0.137	132 (72.1)	131 (74.4)	0.635
Smoking status			0.279			0.474			0.404
Never smoker	118 (30.4)	132 (34.8)		243 (41.4)	268 (44.8)		105 (57.4)	107 (60.8)	
Current smoker	195 (50.3)	169 (44.6)		207 (35.3)	195 (32.6)		37 (20.2)	26 (14.8)	
Former smoker	75 (19.3)	78 (20.6)		137 (23.3)	135 (22.6)		41 (22.4)	43 (24.4)	
Previous MI	10 (2.6)	16 (4.2)	0.208	21 (3.6)	22 (3.7)	0.926	4 (2.2)	16 (9.1)	0.005
Previous PCI	21 (5.4)	33 (8.7)	0.075	59 (10.1)	73 (12.2)	0.238	27 (14.8)	35 (19.9)	0.211
Previous CABG	3 (0.8)	3 (0.8)	1.000	4 (0.7)	4 (0.7)	1.000	4 (2.2)	3 (1.7)	1.000
Previous stroke	1 (0.3	4 (1.1)	0.212	8 (1.4)	5 (0.8)	0.384	5 (2.7)	7 (4.0)	0.568
Familial history of CAD	27 (7.0)	33 (8.7)	0.367	39 (6.6)	43 (7.2)	0.7111	12 (6.6)	13 (7.4)	0.837
Clinical presentation			0.081			0.507			0.005
STEMI	73 (18.8)	59 (15.6)		70 (11.9)	84 (14.0)		30 (16.5)	10 (5.7)	
Non-STEMI	115 (29.6)	94 (24.8)		150 (25.6)	143 (23.9)		38 (20.8)	40 (22.7)	
Unstable angina	200 (51.5)	226 (59.6)		367 (62.5)	371 (62.0)		115 (62.8)	126 (71.6)	
Medication at discharge									
Aspirin	381 (99.2)	379 (100)	0.249	581 (99.1)	585 (98.7)	0.415	177 (97.3)	174 (98.9)	0.449
Beta-blocker	229 (59.8)	206 (54.5)	0.144	319 (54.6)	312 (52.8)	0.529	102 (56.4)	95 (54.9)	0.831
ACEI or ARB	229 (59.8)	198 (52.5)	0.043	321 (54.9)	335 (56.7)	0.532	121 (67.6)	101 (58.4)	0.078
Calcium channel blocker	87 (22.7)	74 (19.6)	0.289	127 (21.7)	121 (20.5)	0.614	47 (26.0)	43 (24.9)	0.903
Statin	372 (97.1)	361 (95.5)	0.234	561 (95.9)	557 (94.2)	0.191	162 (89.5)	162 (93.6)	0.184

Values are mean, mean ± SD, or n (%).

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BMI, body mass index; CABG = coronary artery bypass graft; CAD = coronary artery disease; eGFR = estimated glomerular filtration rate; MI = myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

RENAL FUNCTION CALCULATION AND CLINICAL OUTCOMES. The estimated glomerular filtration rate (eGFR) was calculated using the Cockcroft-Gault equation (mL/min).[12,13] The detailed formula is described in the Supplemental Appendix. Variables included in the eGFR were collected during screening for enrollment. Patients with unavailable eGFR values were excluded from this analysis. We categorized the participants into 3 groups: eGFR above 90 mL/min (high eGFR), eGFR from 60 to 90 mL/min (intermediate eGFR), and eGFR below 60 mL/min (low eGFR).

We analyzed bleeding outcomes, ischemic outcomes, and net adverse clinical events (NACE) at 1 year after the index procedure. The bleeding outcome counted grade 2 or higher events according to Bleeding Academic Research Consortium (BARC) criteria. The ischemic outcome counted cardiovascular death, myocardial infarction (MI), stent thrombosis, repeated revascularization, and ischemic stroke at 1 year. NACE was a composite of all-cause death, BARC 2 or greater bleeding, MI, stent thrombosis, repeated revascularization, and ischemic stroke at 1 year. All clinical outcomes followed the definitions of the Academic Research Consortium.[14] All clinical events were adjudicated by an independent event adjudication committee who were unaware of the treatment allocations.

In addition, we calculated the "probability risk ratio" of bleeding to ischemia for each patient. The ratio was calculated by dividing the bleeding hazard function by the ischemic hazard function as estimated by Cox proportional hazard regression analysis.[15]

STATISTICAL ANALYSIS. The baseline characteristics are presented as mean ± SD for continuous variables and n (%) for categoric variables. For comparison between groups, unpaired Student's *t*-test was applied for continuous variables, and chi-square test (or Fisher exact test when more than

TABLE 2 Clinical Outcomes According to Renal Function and Antiplatelet Therapy Strategy

	High eGFR (n = 767)			Intermediate eGFR (n = 1,185)			Low eGFR (n = 359)			
	De-Escalation (n = 388)	Conventional (n = 379)	*P* value	De-Escalation (n = 975)	Conventional (n = 977)	*P* Value	De-escalation (n = 183)	Conventional (n = 176)	*P* Value	*P* Value for Interaction
Bleeding outcome										
BARC grade ≥2	8 (2.1)	16 (4.3)	0.084	17 (2.9)	34 (5.8)	0.018	8 (4.6)	19 (11.1)	0.024	0.646
BARC grade ≥3	2 (0.5)	2 (0.5)	0.974	5 (0.9)	2 (0.3)	0.250	1 (0.6)	4 (2.3)	0.170	0.232
Ischemic outcome[a]	9 (2.4)	15 (4.0)	0.189	22 (3.8)	24 (4.1)	0.811	12 (6.9)	8 (4.6)	0.377	0.119
NACE[b]	18 (4.7)	31 (8.4)	0.042	41 (7.1)	58 (9.9)	0.085	21 (12.0)	27 (15.6)	0.290	0.508
Target lesion failure[c]	5 (1.3)	7 (1.9)	0.526	6 (1.0)	8 (1.4)	0.610	8 (4.6)	5 (2.9)	0.415	0.294
Deaths										
All-cause death	3 (0.8)	3 (0.8)	0.972	4 (0.7)	6 (1.0)	0.538	1 (0.5)	5 (2.9)	0.095	0.182
Cardiac death	1 (0.3)	2 (0.5)	0.550	1 (0.2)	5 (0.8)	0.106	0 (0.0)	3 (1.7)	0.079	0.261
Nonfatal MI	2 (0.5)	2 (0.5)	0.972	1 (0.2)	4 (0.7)	0.183	4 (2.3)	2 (1.2)	0.428	0.511
Stent thrombosis	0 (0.0)	1 (0.3)	0.313	0 (0.0)	2 (0.3)	0.161	1 (0.5)	0 (0.0)	0.327	0.914
Repeated revascularization	8 (2.1)	13 (3.5)	0.239	16 (2.8)	17 (2.9)	0.891	11 (6.3)	7 (4.1)	0.352	0.124
Target vessel	4 (1.1)	8 (2.2)	0.223	9 (1.6)	5 (0.9)	0.171	8 (4.6)	3 (1.8)	0.135	0.040
Target lesion	4 (1.1)	4 (1.1)	0.963	5 (0.9)	4 (0.7)	0.723	6 (3.4)	3 (1.8)	0.327	0.464
Nontarget vessel	5 (1.3)	7 (1.9)	0.524	9 (1.5)	13 (2.2)	0.414	5 (2.9)	5 (2.9)	0.971	0.641
Stroke	1 (0.3)	1 (0.3)	0.983	6 (1.0)	5 (0.9)	0.748	2 (1.1)	2 (1.2)	0.972	0.973
Ischemic stroke	0 (0.0)	1 (0.3)	0.310	5 (0.9)	3 (0.5)	0.468	1 (0.6)	0 (0.0)	0.324	0.251
Hemorrhagic stroke	1 (0.3)	0 (0.0)	0.325	1 (0.2)	2 (0.3)	0.568	1 (0.6)	2 (1.2)	0.617	0.264

Values are n (Kaplan-Meier estimate, %). [a]Composite of cardiovascular death, MI, stent thrombosis, repeated revascularization, and ischemic stroke. [b]Composite of all-cause death, MI, stent thrombosis, repeated revascularization, ischemic stroke, and BARC ≥2 bleeding events. [c]Includes cardiac death, target lesion revascularization, and target vessel MI.

BARC = Bleeding Academic Research Consortium; eGFR = estimated glomerular filtration rate; MI = myocardial infarction; NACE = net adverse clinical event(s).

20% of expected count was <5) was applied for categoric variables. For comparison among 3 groups, 1-way analysis of variance was applied for continuous variables. The cumulative incidence of clinical outcome was calculated by means of Kaplan-Meier analysis, and the log-rank test was performed to compare the group differences. The HR and 95% CI were calculated from the Cox proportional hazard regression analysis. Covariates that were considered to be clinically meaningful were included to calculate multivariate-adjusted HR and its 95% CI. Age, sex, body mass index, presence of hypertension, diabetes mellitus, clinical diagnosis of ACS, and history of MI were included. The estimated clinical outcome risk was obtained by means of multivariate Cox proportional hazard regression analysis. The probability risk ratio was obtained by dividing ischemic hazard function from the bleeding hazard function. All *P* values were 2-sided, and $P < 0.05$ was considered to be statistically significant. Statistical tests were performed using SPSS version 26 and R programming language version 3.6.3.

RESULTS

BASELINE CHARACTERISTICS. Among the 2,338 patients randomized in the original trial, 27 were excluded because their eGFRs were not available. The cohort for the present analysis included 2,311 patients who were grouped into tertiles according to eGFR (**Figure 1**). The high, intermediate, and low eGFR group included 767, 1,185, and 359 patients, respectively. Patients with decreased renal function had more cardiovascular risk factors, including old age, hypertension, diabetes mellitus, and previous history of PCI or stroke (Supplemental Table 1). The baseline characteristics between the 2 randomization arms according to baseline renal function are presented in **Table 1**. The median follow-up duration was 365 days (IQR: 365-365 days) in both randomization arms. Among patients with low eGFR, those randomized to de-escalation were slightly younger, had less history of MI, and more frequently presented with ST-segment elevation MI compared with those randomized to the conventional treatment. Otherwise, the baseline characteristics were well balanced between the randomized strategies.

CLINICAL OUTCOMES ACCORDING TO RENAL FUNCTION. At 1 year after PCI, the NACE rates increased as the baseline renal function decreased (6.5% vs 8.5% vs 13.7% in the high, intermediate, and low eGFR groups, respectively; $P < 0.001$) (Supplemental Table 2). When the clinical events were divided into bleeding and ischemic events, bleeding events occurred more frequently in patients

TABLE 3 HRs for Bleeding and Ischemic Outcomes Based on eGFR Levels in Prasugrel-Based De-escalation Group

	De-Escalation, Events/Patients (%)	Conventional, Events/Patients (%)	Univariate HR[a] (95% CI)	Multivariate HR[b] (95% CI)	*P* Value for Interaction
Bleeding outcome[c]					
High eGFR	8/388 (2.1)	16/379 (4.3)	0.48 (0.21-1.12); $P = 0.091$	0.48 (0.21-1.13); $P = 0.092$	0.646
Intermediate eGFR	17/587 (2.9)	34/598 (5.8)	0.50 (0.28-0.90); $P = 0.020$	0.50 (0.28-0.90); $P = 0.021$	
Low eGFR	8/183 (4.6)	19/176 (11.1)	0.40 (0.18-0.91); $P = 0.030$	0.36 (0.15-0.83); $P = 0.017$	
Ischemic outcome[d]					
High eGFR	9/388 (2.4)	15/379 (4.0)	0.58 (0.25-1.32); $P = 0.195$	0.61 (0.26-1.39); $P = 0.235$	0.119
Intermediate eGFR	22/587 (3.8)	24/598 (4.1)	0.93 (0.52-1.66); $P = 0.811$	0.95 (0.53-1.69); $P = 0.855$	
Low eGFR	12/183 (6.9)	8/176 (4.6)	1.49 (0.61-3.65); $P = 0.380$	1.18 (0.47-2.98); $P = 0.730$	

Values are events/n (Kaplan-Meier estimate, %). [a]Reference group: Prasugrel-based conventional strategy group. [b]Adjusted for age, sex, body mass index, hypertension, diabetes mellitus, clinical diagnosis of acute coronary syndrome, and previous myocardial infarction. [c]Bleeding outcome: Bleeding Academic Research Consortium grade ≥2 bleeding events. [d]Ischemic outcome: composite of cardiovascular death, myocardial infarction, stent thrombosis, repeat revascularization, and ischemic stroke.

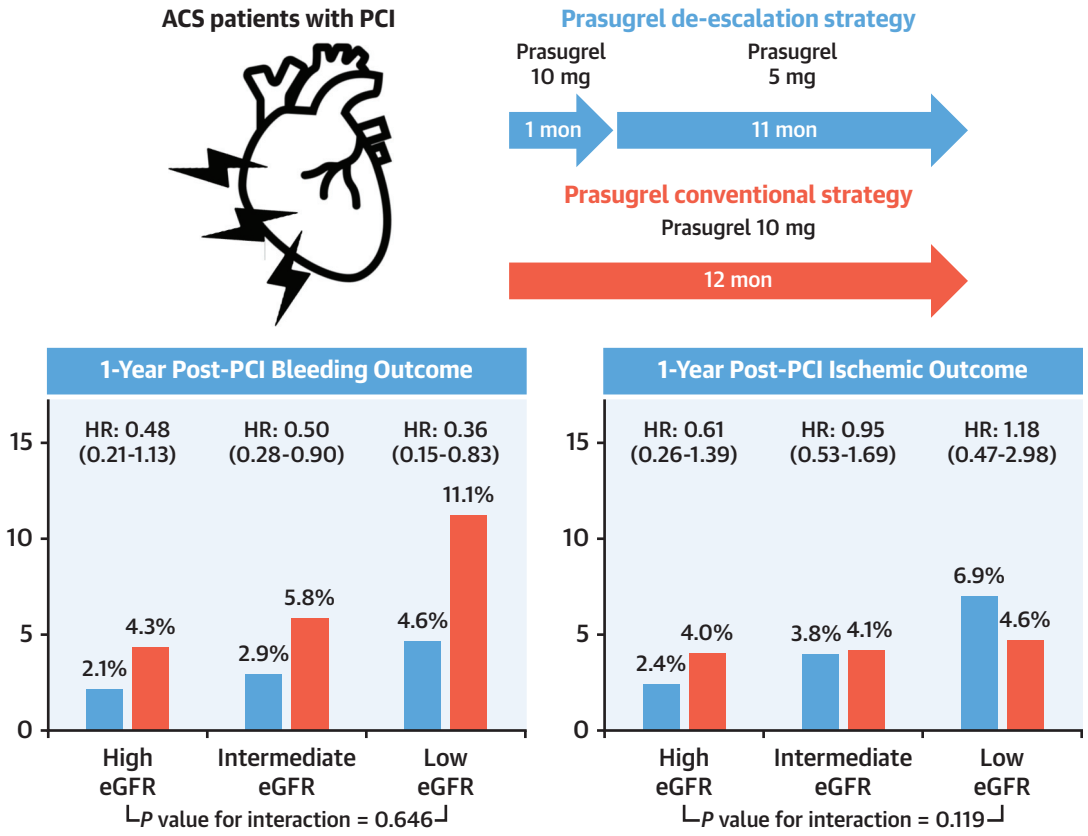
with decreased renal function (3.2% vs 4.4% vs 7.8% in the high, intermediate, and low eGFR groups, respectively; $P = 0.003$) (Supplemental Table 2). Ischemic events also occurred more frequently in those with decreased renal function (3.2% vs 4.0% vs 5.8% in the high, intermediate, and low eGFR groups, respectively; $P = 0.120$) (Supplemental Table 2). **Figure 2** demonstrates the cumulative incidence of bleeding and ischemic events. The associations between continuous eGFR values and the risk of clinical events are presented in Supplemental Table 3. Decreasing eGFR was associated with both bleeding (HR: 1.13 per 10 mL/min eGFR decrease; 95% CI: 1.02-1.25; $P = 0.009$) and ischemic outcomes (HR: 1.18 per 10 mL/min eGFR decrease; 95% CI: 1.06-1.31; $P = 0.040$).

CLINICAL OUTCOMES ACCORDING TO ANTIPLATELET THERAPY STRATEGY AND RENAL FUNCTION. Compared with the conventional dual antiplatelet therapy strategy, prasugrel dose de-escalation was associated with numerically lower rates of NACE regardless of renal function (*P* for interaction = 0.508) (**Table 2,** Supplemental Figure 1). Bleeding occurred more frequently in patients randomized to the conventional strategy in the intermediate and low eGFR groups (intermediate eGFR group 2.9% vs 5.8% [$P = 0.018$] and low eGFR group 4.6% vs 11.1% [$P = 0.024$] for the de-escalation and conventional arms, respectively) (**Table 2**). However, the numerically higher rate of bleeding in the conventional group was not statistically significant in the high eGFR group (high eGFR group 2.1% vs 4.3% for the de-escalation and conventional arms, respectively; $P = 0.084$). In a Cox regression model, prasugrel dose de-escalation reduced bleeding by 50% in the intermediate eGFR group (HR: 0.50; 95% CI: 0.28-0.90; $P = 0.021$), and by 64% in the low eGFR group (HR: 0.36; 95% CI: 0.15-0.83; $P = 0.017$) (**Table 3**). Impact of prasugrel de-escalation did not reach statistical significance in the high eGFR group (HR: 0.48; 95% CI: 0.21-1.13; $P = 0.092$). The reduction of bleeding was consistent without interaction between the antiplatelet therapy strategy and renal function (*P* for interaction = 0.646). However, the magnitude of effect was largest in those with a low eGFR (**Central Illustration**). When we performed a sensitivity landmark analysis at 1 month, the impact of de-escalation in reducing bleeding events was also consistent regardless of baseline renal function (*P* for interaction = 0.671) (Supplemental Table 4).

Regarding the ischemic outcome, the event rates were not significantly different between the de-escalation and conventional strategy in all eGFR groups (high eGFR group 2.4% vs 4.0% [$P = 0.189$], intermediate eGFR group 3.8% vs 4.1% [$P = 0.811$], and low eGFR group 6.9% vs 4.6% [$P = 0.377$] for the de-escalation strategy arm and conventional strategy arm, respectively) (**Table 2**). No significant interaction was observed (*P* for interaction = 0.119) between the prasugrel strategy and renal function (high eGFR group: HR: 0.61 [95% CI: 0.26-1.39; $P = 0.235$]; intermediate eGFR group: HR: 0.95 [95% CI: 0.53-1.69; $P = 0.855$], and low eGFR group: HR: 1.18 [95% CI: 0.47-2.98; $P = 0.730$]) (**Table 3**). Again, a landmark analysis at 1 month showed no significant difference between the 2 strategies in all eGFR subgroups without any interaction (*P* for interaction = 0.133) (Supplemental Table 4).

The association between continuous eGFR values and the risk of clinical events is demonstrated in **Figure 3**. Both bleeding and ischemic risk increased as eGFR decreased regardless of conventional or de-escalation group. However, the bleeding risk increase was more profound with decreasing eGFR in the conventional group compared with the de-escalation group. Regarding ischemic risk, the

CENTRAL ILLUSTRATION **The Impact of Prasugrel-Based De-Escalation According to Renal Function**



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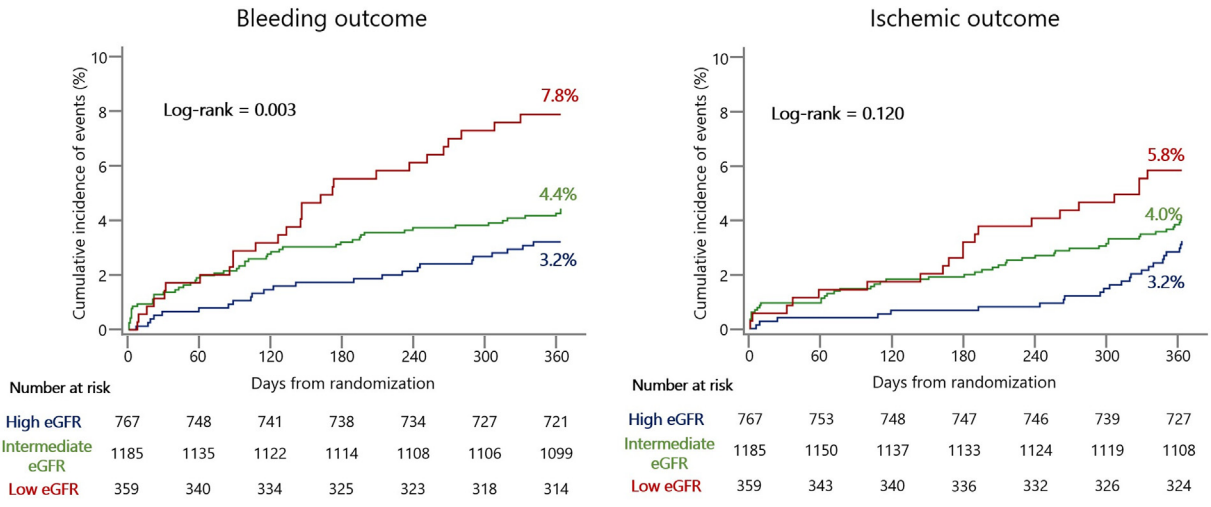
De-escalation strategy reduced bleeding significantly regardless of baseline renal function. There was no significant increase in ischemic events in return for reduced bleeding among all eGFR groups. Values are HR (95% CI). ACS = acute coronary syndrome; eGFR = estimated glomerular filtration rate; PCI = percutaneous coronary intervention.

difference was not significant between the 2 groups and increased similarly as eGFR decreased.

RELATIVE TRADE-OFF BETWEEN ISCHEMIC AND BLEEDING RISKS: PROBABILITY RISK RATIO. We calculated the "probability risk ratio" to evaluate the relative trade-off between bleeding and ischemic risk by antiplatelet therapy strategy in each individual patient. Figure 4 demonstrates the distribution of the probability risk ratio according to renal function and the randomized strategy. The probability risk ratio increased with decreasing renal function (1.06 vs 1.26 vs 1.36 for high, intermediate, and low eGFR groups, respectively; P for trend <0.001), suggesting higher relative bleeding risk than ischemic risk in those with impaired renal function. Within each eGFR group, the probability risk ratio was significantly higher in those randomized to the conventional strategy compared with the de-escalation strategy (1.24 vs 0.89, 1.67 vs 0.84, and 1.94 vs 0.80 for high, intermediate, and low eGFR groups, respectively; all $P < 0.001$). Furthermore, within those randomized to the de-escalation strategy, the mean probability risk ratio was not significantly different according to renal function (0.89 vs 0.84 vs 0.80 for high, intermediate, and low eGFR groups, respectively; P for trend = 0.053), which was in contrast to those randomized to the conventional strategy, where the mean probability risk ratio increased significantly as renal function decreased (1.24 vs 1.67 vs 1.94 for high, intermediate, and low eGFR groups, respectively; P for trend <0.001). Accordingly, the difference of the probability risk ratio between the 2 strategies was the

FIGURE 2 **Cumulative Incidence of Clinical Outcomes According to Kidney Function**



A depressed estimated glomerular filtration rate (eGFR) was associated with significant increase in bleeding outcome, whereas a depressed eGFR was associated with increase in ischemic outcome with marginal significance.

largest in the low eGFR group (difference in risk ratio 0.36 vs 0.83 vs 1.13 for high, intermediate, and low eGFR groups, respectively).

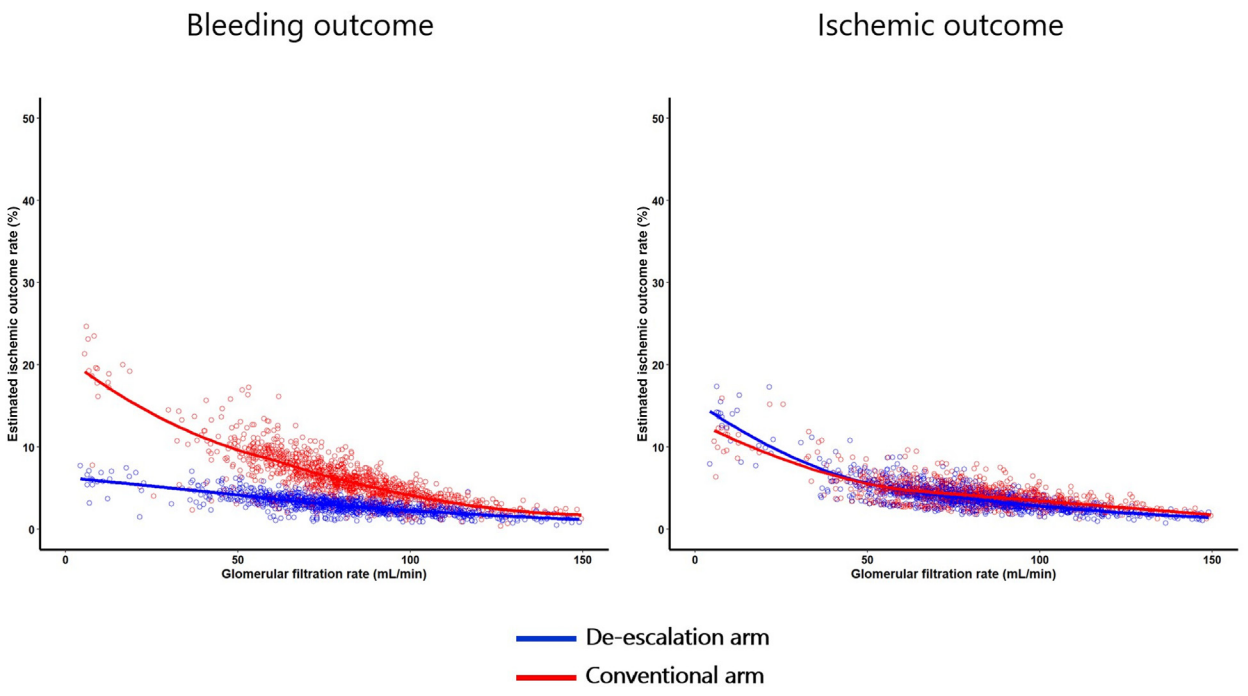
DISCUSSION

The principle finding from this post hoc analysis of the HOST-REDUCE-POLYTECH-ACS trial are as follows: 1) The rates of both bleeding and ischemic events increased as renal function decreased; 2) prasugrel dose de-escalation significantly reduced bleeding risk without a significant increase in ischemic events, regardless of the renal function; 3) the net benefit of the de-escalation strategy was consistent regardless of renal function; and 4) the relative risk trade-off between ischemia and bleeding suggested significantly increased risk of bleeding as renal function decreased in those randomized to the conventional arm. However, the balance was relatively neutral and relatively consistent regardless of the renal function in those randomized to the de-escalation arm.

CLINICAL OUTCOMES WITH IMPAIRED RENAL FUNCTION. Impaired renal function is a well-known risk factor for adverse outcomes in those receiving PCI for ACS.[5] As we tackle more complex lesions and patients, the prevalence of impaired renal function in our practice is increasing. Previous studies reported that patients with impaired renal function had greater risk of both bleeding and ischemic events compared with those with preserved renal function.[2,3] Latif et al reported a stepwise increase in both cardiovascular events and bleeding complications with decreased renal function in patients receiving PCI.[2] In the PROMETHEUS study, the presence of CKD was associated with a greater risk for major adverse cardiac events at 1 year, and bleeding complications were frequent in patients with CKD.[3] In line with these previous studies, our study showed that decreased renal function was associated with a higher risk for NACE, a composite of both bleeding and ischemic events. Considering the opposite nature of bleeding and ischemic events, some plausible explanations for the simultaneously increased risk have been raised. This includes increased systemic inflammation, oxidative stress, and endothelial dysfunction in patients with impaired renal function.[5,16] One study suggested that platelet dysregulation played a central role in driving inflammation, thrombosis, and bleeding in CKD.[16]

ANTIPLATELET STRATEGY WITH IMPAIRED RENAL FUNCTION. Owing to the elevated risk for both bleeding and ischemic events, reports of the potential benefit or harm of potent P2Y12 inhibitors such as prasugrel in patients with impaired renal function have shown conflicting results.[3,5,7,17] In a subgroup analysis of the TRITON-TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by

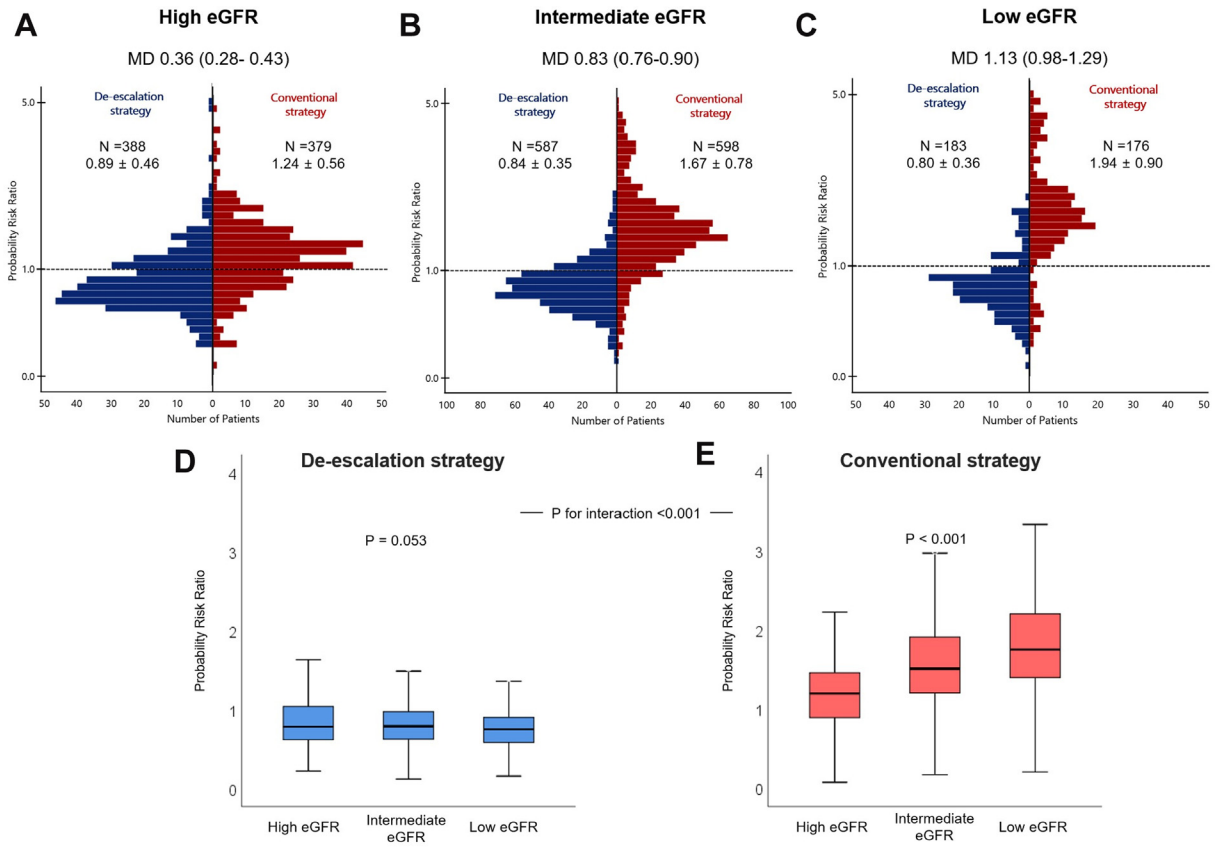
FIGURE 3 Continuous Association Between Estimated Glomerular Filtration Rate and Risk of Clinical Outcomes



Continuous association between the estimated glomerular filtration rate and clinical outcomes is demonstrated according to antiplatelet strategy. The estimated clinical event rate was calculated from the multivariate adjusted Cox proportional hazard regression model, which included the covariates that were considered clinically meaningful.

Optimizing Platelet Inhibition With Prasugrel-Thrombolysis In Myocardial Infarction 38; NCT00097591), a large randomized clinical trial comparing prasugrel and clopidogrel in ACS patients receiving PCI, 1,490 patients with decreased creatinine clearance showed similar benefit to the overall population, but no data were available about the bleeding complications of that subgroup.[7] On the other hand, the PROMETHEUS study, a multicenter observational study, reported that outcomes with prasugrel use were not significantly improved compared with clopidogrel in patients with CKD, owing to the similar increase and thus trade-off between major clinical adverse events and bleeding complications.[3] In the present study, the benefit of the de-escalation strategy was consistent regardless of baseline renal function. Although there was no significant interaction between the prasugrel strategy and renal function on the net clinical adverse events, the benefit of de-escalation was different according to eGFR group. The benefit of de-escalation for bleeding showed an increasing trend as renal function decreased. In the high eGFR group, although bleeding events were numerically higher in the conventional group, the reduction in bleeding risk with de-escalation was not significant, mainly because the number of bleeding events per se in the high eGFR group was low. In the low eGFR group, de-escalation was associated with a similarly statistically insignificant but numerically higher rate of ischemic events which was mainly driven by increase in revascularization. In terms of hard end points, the rates numerically favored the de-escalation group (hard ischemic events such as cardiovascular death, nonfatal MI, and ischemic stroke occurred more frequently in the conventional group, also without statistical significance). The small number of events prohibit any statistically meaningful comparisons. However, the profound reduction in bleeding risk resulted in a consistent overall benefit for de-escalation. This study suggests that de-escalation may be a feasible strategy even in patients with chronic kidney disease and ACS. Recently, the subanalysis of TWILIGHT (Ticagrelor With Aspirin or

FIGURE 4 **Probability Risk Ratio (of Bleeding to Ischemia) Based on Estimated Glomerular Filtration Rate (eGFR) Levels**



(A to C) Probability risk ratio was calculated by dividing bleeding outcome risk by ischemic outcome risk for each patient. Bleeding and ischemic outcome risks were obtained by means of multivariate Cox proportional hazard regression analysis. The probability risk ratio was significantly higher in those randomized to the conventional strategy compared with the de-escalation strategy among all eGFR groups. **(D and E)** Box and whisker plots for the probability risk ratios. The **box** represents the interquartile range, **whiskers** extend to the most extreme data point that is no more than 1.5 times the interquartile range from the **box**, and the **line within the box** represents the median value. Lower eGFR was associated with higher probability risk ratio (greater relative risk of bleeding compared with ischemia) in patients randomized to the conventional strategy. However, in those randomized to the de-escalation strategy, there were no significant differences in the probability risk ratio among the 3 eGFR groups. There was significant interaction between the antiplatelet therapy strategy and the effect of eGFR on probability risk ratio (*P* for interaction <0.001). MD = mean difference.

Alone in High-Risk Patients After Coronary Intervention) study, which assessed the benefit of ticagrelor monotherapy among patients with CKD and undergoing PCI, showed ticagrelor monotherapy reduced bleeding events without a significant increase in ischemic events compared with ticagrelor plus aspirin.[18] That study is in line with our study, favoring de-escalation strategy in patients with impaired renal function.

In addition, we calculated the probability risk ratio to evaluate the bleeding-ischemia trade-off by prasugrel dose strategy. This value was largest in those with low eGFR, confirming that those with a lower eGFR have a relatively greater bleeding risk compared with ischemic risk. The relative risk trade-off between ischemia and bleeding significantly tilted toward bleeding in the conventional arm as renal function decreased. However, the balance was relatively neutral and consistent regardless of the renal function in the de-escalation arm. In the low eGFR group, the bleeding risk was increased by the conventional strategy, while the ischemic risk was not increased by the de-escalation strategy. Collectively, our results suggest that the benefit of de-escalation may be greatest in patients with CKD.

The rationale of the current de-escalation strategy is to maximize ischemic risk reduction by using a conventional dose of prasugrel in the first month after PCI, when the thrombotic risk is greatest, and to minimize the bleeding risk thereafter by deescalating

to a lower dose of prasugrel in the chronic phase.[19-22] Because patients with impaired renal function are known to have higher platelet reactivity, potent P2Y12 inhibitors may have significant benefit especially in the early phase in these patients.[22-24] However, owing to the coexisting high bleeding risk, continuation of the standard dose of prasugrel in the chronic phase might aggravate the bleeding risk, which might lead to a higher mortality rate.[8,9] Therefore, a conventional dose of prasugrel for one month followed by a de-escalation may be good balance to minimize ischemic and bleeding events.

STUDY LIMITATIONS. First, this study is a post hoc analysis of the HOST-REDUCE-POLYTECH-ACS study. The trial was neither designed nor powered to answer whether de-escalation was the optimal strategy for ACS patients with CKD receiving PCI. Furthermore, the number of patients with low eGFR was small. Therefore, the results of the present analysis should be considered as only hypothesis generating. Second, the creatinine levels were measured at only a single time point before the procedure, limiting ability to discriminate progressive CKD and acute kidney injury. Third, this study was performed in an East Asian population, and therefore extrapolation of the current findings to other ethnicities may be difficult considering that the East Asian population may have characteristics that make this population more prone to bleeding than ischemia.[15,25] However, with all its inherent limitations, we think that these results suggest important clues on how to approach patients with decreased renal function who may be at increased risk of both bleeding and ischemia.[5,26]

CONCLUSIONS

Patients with impaired renal function who present with ACS and receive PCI are at high risk for both ischemic events and bleeding events. The beneficial effect of prasugrel-based de-escalation strategy was consistent regardless of the baseline renal function, mostly driven by a reduction in bleeding risk, which was greatest in those with low eGFR.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: HOST-REDUCE-POLYTECH-ACS reported the benefit of prasugrel-based de-escalation strategy in patients with ACS receiving PCI. In this subgroup analysis of HOST-REDUCE-POLYTECH-ACS, prasugrel-based de-escalation strategy was beneficial regardless of baseline renal function.

TRANSLATIONAL OUTLOOK: Our study found a signal of larger bleeding risk reduction with prasugrel-based dose de-escalation in patients with lower renal function. Further studies are necessary to validate our hypothesis.

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KEY WORDS acute coronary syndrome, chronic kidney disease, prasugrel

APPENDIX For the Cockcroft-Gault Equation and supplemental tables and a figure, please see the online version of this paper.